



Review Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM - AN INNOVATIVE APPROACH FOR ENHANCEMENT OF SOLUBILITY AND THERAPEUTIC POTENTIAL

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ABSTRACT:

Purpose: As the development of modern drug discovery techniques, there has been increase in the number of pharmaceutical compounds that are poorly water soluble. These lipophilic compounds possess low dissolution rate and therefore low bioavailability. The Formulation scientists should adopt various strategies to enhance their absorption. This paper is an insight for improving the solubility of poorly water soluble compounds.

Approach: Lipidic formulations are found to be a promising approach to combat the solubility challenges. Self MicroEmulsifying Drug Delivery Systems (SMEDDS) are gaining more attention for improving the solubility of the lipophilic drugs.

Findings: SMEDDS are isotropic mixtures of oil, surfactant and co surfactant and are vital tool in solving low bioavailability problems of poorly soluble drugs. Lipophilic drugs can be dissolved in these systems, enabling them to be administered per orally. When this is released into the lumen it results in w/o microemulsion with the aid of G.I fluid.

Conclusion: This present review describes various formulation components, mechanism of emulsification, biopharm aspects, characterization methods and application of SMEDDS.

Key words: surfactants, solubility, SMEDDS, microemulsion.

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INTRODUCTION

The fact that 40-70% of the new chemical entities which are discovered and many existing drug molecules possess insufficient aqueous solubility which leads to poor bioavailability. This presents a serious challenge to formulate & market new drugs in the pharma industry.¹

Many formulation approaches are employed to improve the solubility of the drugs. One of the most popular approaches is the incorporation of the

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active lipophilic component into inert lipid vehicle such as oils, surfactant dispersions, self emulsifying formulations, liposome, polymeric nanoparticles, solid lipid nanoparticles, micro emulsion. A detailed classification of various lipid vehicles and their subclasses are shown in Figure 1.

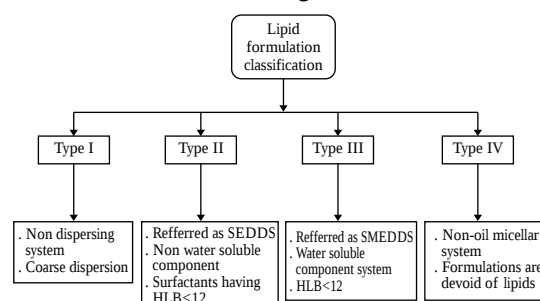


Fig 1: Classification of various lipid vehicles and their subclasses

Self emulsifying drug delivery system is one among the methods used for lipophilic drugs which are associated with poor water solubility & low bioavailability. SMEDDS are isotropic mixtures of oils surfactants and co-surfactants/co solvents that have an ability to form oil-in-water micro emulsion upon agitation followed by dilution in aqueous media such as gastro intestinal fluids. The motility of the stomach and intestine provide the agitation necessary for self emulsification.² This systems can exists as self emulsifying drug delivery system [SEDDS] and self micro emulsifying drug delivery system [SMEDDS]. Both SEDDS and SMEDDS have distinct features associated with improved drug delivery properties. SEDDS are simply binary systems with lipophilic phase and the drug.

The formation of SMEDDS requires the use of co-surfactant to generate micro emulsion. SEDDS produce opaque emulsion with a droplet size of 100 to 500 nm, while SMEDDS form translucent micro emulsion with a droplet size of <50 nm SMEDDS are physically stable formulations that are easy to manufacture.^{3,4} A diagrammatic representation of SMEDDS has shown in Figure 2.

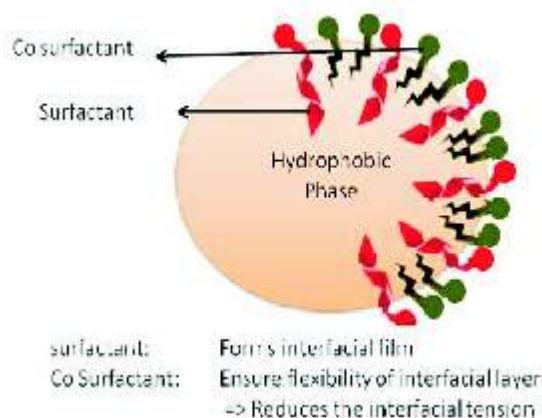


Fig 2: Diagrammatic representation of SMEDDS

ADVANTAGES OF SMEDDS:⁵

- ◆ Protection of drug against GIT environment.
- ◆ Enhanced oral bioavailability.
- ◆ Ease of manufacture and scale up
- ◆ Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- ◆ Better drug delivery profiles.
- ◆ Reduced intra subject and inter subject variability including food effects.
- ◆ High drug loading capacity

DISADVANTAGES OF SMEDDS:⁶

- ◆ One of the obstacles for the development of SMEDDS is the lack of good predictive in vitro model for assessment of the formulations.
- ◆ Traditional dissolution doesn't work, because these formulations are dependent on digestion prior to the release.
- ◆ The in vitro models need further development and validation before its strength can be evaluated.
- ◆ Further development will be based on the in vitro – in vivo correlation and therefore different prototype lipid based formulation needs to be developed and tested in vivo in a suitable animal model.
- ◆ Volatile solvents present in formulation may migrate onto the capsule shells, results in the precipitation of the lipophilic drugs.
- ◆ As the formulation contains several components, validating becomes a greater challenge.
- ◆ Chemical instability and high concentration of surfactant in the formulation cause irritation in the GI tract.

PROPERTIES OF SMEDDS:^{7,8}

- ◆ They form an o/w emulsion rapidly in GI fluids, under the influence of gentle agitation provided by the peristaltic movements of GI tract.
- ◆ They can effectively incorporate both hydrophobic & hydrophilic drugs within oil surfactant mixture.
- ◆ They can be presented as both liquids as well as solid dosage forms.
- ◆ They require lower dose of drug with respect to conventional oral dosage form.

FACTORS INFLUENCING THE FORMULATION OF SMEDDS:^{9,15}

Drug dose:

Generally drugs which are administered with a high dose are not accepted for SMEDDS, unless they show extremely good solubility in any one of the components of SMEDDS preferably lipophilic phase. The drugs which are not soluble in oil/water and having a log p value around 2 are not suitable candidate for SMEDDS.

Oil phase solubility:

Solubility of the drug in the oil phase is greatly influenced by the ability of the SMEDDS to maintain the drug in the solubilized form. When the drug is solubilized by the use of surfactant and co surfactant then there could be a risk of precipitation, as dilution of SMEDDS can lead to lowering of solvent capacity, there by resulting in precipitation.

Polarity and lipid phase:

The polarity of the lipid phase is the most important factor that influences the release of the drug from the micro emulsion. HLB, chain length, degree of unsaturation of fatty acid, molecular weight of the lipid & concentration of the emulsifier are the factors that govern the polarity of the droplet. The high polarity will promote the rapid rate of release into the aqueous phase. The highest release was obtained with the formulation that had oily phase with highest polarity

Charge on emulsion droplet:

Absorptive cells and other cells in the body are negatively charged compared to the mucosal solution in the lumen. The positively charged emulsion droplets are formed by adding oleylamine and undergo electrostatic interactions with the caco 2 monolayer. The positively charged emulsion will increase the self micro emulsifying oily formulations.

MECHANISM OF EMULSIFICATION:^{8,4}

According to Reiss, self emulsification occurs when the entropy change is greater than the energy required to increase the surface area of the dispersion. Self emulsifying process is related to the free energy. The free energy of the conventional emulsion is a direct function of the energy required to create new surface between oil and water phases and can be described by the equation

$$DG = SN_p r^2, \text{ where}$$

DG = free energy associated with the process

N = is the number of droplets of radius 'r'

S = is the interfacial energy.

It is the evident from the above equation that spontaneous formation of interface between oil and water phase is not favorable due to higher energy level. Two phases will tend separate with time to

reduce the interfacial area & the emulsion will be stabilized by emulsifying agents and reduces the interfacial energy as well as providing a barrier to prevent coalescence.

EXCIPIENTS USED IN FORMULATION:^{10,11,12}

Many studies have revealed that the self micro emulsification process is specific to the nature of oil/surfactant ratio; oil/surfactant pair; surfactant concentration; concentration and nature of co-surfactant; surfactant and co-surfactant ratio and temperature at which the self micro emulsification occurs. Use of other excipients in the SMEDDS is governed by the type of dosage form. The formulated SMEDDS is specific to the particular drug only.

Various major components of SMEDDS are:

- ◆ Oils
- ◆ Surfactant
- ◆ Co-surfactant
- ◆ Co solvent

OILS:

Generally oil with a long chain tri glyceride and medium chain tri glycerides with varying degree of saturation have been used for the formulation of SMEDDS. Some of the marketed formulations and the oily phases used for the same is given in Table 1. Unmodified edible oils provide the natural base for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative emulsification efficiency reduce their use in SMEDDS. Therefore modified or hydrolyzed vegetable oils are preferred as compared to natural edible oils. Medium chain triglycerides can be replaced by novel semi synthetic medium chain triglycerides such as –gelucire due to their higher fluidity, better solubility and self emulsification ability. A generalized list of oils/lipids that can be used in formulating SMEDDS is given in the table 2.

TABLE 1: Types of oils used in SMEDDS:

Type of oil	Drug
Transcutol	Candesartan cilexetil
Castor oil	Valsartan
Sefsol 218/oleic acid	Atorvastatin
Ethyl oleate/ medium chain triglyceride	Silymarin
Labrafil M 1944 CS	Cyclosporine A

TABLE 2: List of oils that can be used in SMEDDS:

CLASS	EXAMPLES
TRIGLYCERIDE VEGITABLE OIL-	
• Triglycerides of long chain fatty acids	Soyabean oil, peanut oil, corn oil
• Triglycerides of medium chain fatty acids	Miglyol 812, captex 355, labrafac
VEGETABLE OIL DERIVATIVES-	
• Hydrogenated vegetable oil	Hydrogenated cotton seed oil
• Mixed partial glycerides	Capmul MCM
• Poly oxy glycerides/macrogol glycerides	Labrafil 1944CS, labrafil M 2125CS, labrasol, gelucire44/14
• Ethoxylated glycerides	Cremophor EL, cremophoreRH40, cremophorRH60
• Poly alcohol esters of fatty acids	Plurol oleiqueCC497, capryol, mirj.
FATTY ACIDS	Oleic acid, myristic acid, caprylic acid, capric acid.
ETHANOL ESTER	Ethyl oleate.

SURFACTANTS:

Surfactant is obligatory to provide the essential emulsifying characteristics to the SMEDDS. Surfactant being amphiphilic in nature can dissolve relatively high amount of hydrophobic drug compounds. Surfactant from natural origin is much safer than the compounds of synthetic origin. The two factors that are considered for selection of surfactants is HLB & safety. Surfactant of high HLB is selected because they impart high emulsifying capacity. Types of surfactants used in commercial formulations are mentioned in table 3. A detailed list of surfactants with their HLB values is given in table 4.

TABLE 3: Types of surfactants used in SMEDDS:

TYPE OF SURFACTANT	DRUG
Tween 80	Domperidone
Cremophor EL	Exemestane
Span 20	Loratidine
D-a-tocopheryl polyethylene glycol1000 succinate	Fenofibrate
Tween 20	Glyburide

TABLE 4: List of surfactants with HLB values:

CHEMICAL OR COMMAN NAME	TRADE NAME	HLB
Poly oxy ethylene 20 sorbitan monolaurate	Poly sorbate 20	16-17
PEG 1500	Lauric glycerides	14
PEG 400 capric/caprylic glycerides	Labrasol	14
Polyoxyl 35 castor oil	Cremophor EL	12-14
Polyoxyl 40 hydrogenated castor oil	Cremophor RH 40	14-16
Unsaturated polyglycolized glycerides	Labrafil MI 21255	4
Saturated polyglycolized glycerides	Gelucire 44/14 59/13	13-14
Poly oxy ethelene lauryl ether	Brij 35	13.7
Poly oxyl 40 stearate	Myrij 52	16.9

The possible mechanism by which the surfactants acts include-

Improved drug dissolution,

Increased intestinal wall permeability

Increased tight junction permeability &

Decreased / inhibited p-glycoprotein drug efflux.

But large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate GI tract.

CO-SURFACTANT:

Co-surfactants is added mainly to lower the interfacial tension between the oil and water phase and allows spontaneous formulation of micro emulsion. In SMEDDS generally

co-surfactant of HLB value 10-14 are used. Examples of co-surfactants used in marketed formulation is given in table 5

TABLE 5: Type of co-surfactants used in SMEDDS:

TYPE OF COSURFACTANT	DRUG
Lutrol E400	Cefuroxime axetil
Transcutol	Acyclovir
Propylene glycol	Mebendazole
PEG 400	Feno fibrate
Ethanol	Curcumin

FORMULATION DESIGN:^{13,14}

1. SCREENING OF EXCIPIENTS:

The following parameters must be considered during the formulation of SMEEDS.

Solubility of the drug in different oil, surfactants, and co-surfactants.

The selection of suitable oil, surfactant, co-surfactant and preparation of phase diagram.

SOLUBILITY STUDIES:

These studies are generally performed with the objective of choosing an oil, surfactant and co surfactant that shows maximum capacity to solubilize the drug. The solubility of the drugs in various oils, surfactants and co-surfactants is determined by shake flask method. In this method, the drug is usually added to the excipients in excess amount and then shaken for 48 hours in water bath or in air oscillator at room temperature. Then samples are subjected to centrifugation followed by filtration through 0.45µm filter and drug content is determined.

SCREENING OF SURFACTANT AND CO-SURFACTANT FOR SELF EMULSIFICATION ABILITY.¹⁵

Here the oil and surfactant is mixed in equal proportion, and subsequently homogenized and tested for its self emulsification ability when added to double distilled water. The number of flask inversions required to form a homogeneous emulsion is noted and this give an indication about the ease of emulsification. The resulted microemulsion should be tested for clarity, turbidity & percentage transmittance. The surfactants which show high percentage of transmittance and that require low flask inversions should be selected. The same procedure can be adopted for screening of co surfactants by mixing with selected surfactant and oil phase.

2. CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM:¹⁵

Phase diagrams represent the change in phase behavior of the system according to the change in composition. The ternary diagram consists of 3 corners correspond to 100% of the particular component. In case of addition of fourth component, the ternary phase diagram can be called as pseudo ternary phase diagram, as one of the corners of the diagram correspond to the mixture of two components like surfactant and co-surfactant. In SEDDS the system consists of three components like oil, surfactant & water where as in case of SMEDDS an additional component co-surfactant is most common.

For the construction of the pseudo ternary phase diagram, mixture containing different compositions of micro emulsion components should be evaluated for emulsification efficiency. The diagram is constructed by keeping the ratios of any two of the four components as constant and ratio along with the other two components forms three corners of the phase diagram which is shown in figure 3. This mixture may be the combination of surfactant and co-surfactant or sometimes the mixture of oil & surfactant. This mixture is mixed with the required quantity of third phase like oil or co-surfactant, the other component water is added in incremental amount. For each addition of fourth component, the solution should be tested for the clarity, flowability,

self emulsification time, dispersibility. The total % concentration of all components should be 100%. Generally this diagram is plotted using suitable software. The sample which forms a clear solution should be denoted by suitable symbols in the phase diagram. The area that is formed after joining the points indicates the monophasic microemulsion. Existing area and wide area indicate the good emulsification efficiency of the system.

3. PREPARATION OF SMEDDS:

The methods used for preparing the microemulsion for improving the bioavailability of the drugs and formulation by emulsifying the drug with the self micro emulsifying excipients can be described by following methods.

1. Phase titration method
2. Phase inversion method

Phase titration method/ water titration method:¹⁶

Micro emulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of a constructed phase diagram. This is a useful approach to the study the complex series of interactions that can occur when different components are mixed. A mixture of fatty acid and oil is mixed to a caustic solution in order to prepare micro emulsion, and then it is titrated with the co-surfactant the system turns clear. Micro emulsion will be formed with various associated structures such as emulsion, micelles, lamellar, cubic, various gels and oily dispersions. Depending on the chemical composition and concentration of each component pseudo ternary phase diagram is constructed instead of quaternary phase diagram to find the different zones including micro emulsion zone, in which each corner of the diagram represent 100% of the particular component. The region can be separated into w/o or o/w micro emulsion by considering the composition that is oil rich or water rich. Observations should be made carefully so that metastable systems are not included.

Phase inversion method:¹⁷

The phase inversion occurs as a result of addition of excess amount of dispersed phase. During phase inversion quick physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of

spontaneous changing of curvature of surfactant. For non-ionic surfactant the inversion can be accomplished by changing the temperature, forming a transition from an o/w microemulsion to w/o microemulsion at a high temperature.

During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is known as phase inversion temperature. Additionally a transition is the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets will be formed in a continuous oil phase. Increasing the water volume fraction, changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at inversion locus.

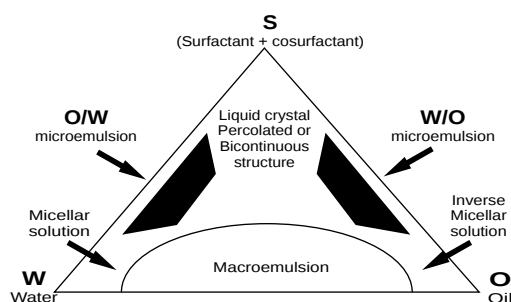


Fig 3: Pseudo ternary phase diagram¹⁷

4. CHARACTERIZATION OF SMEDDS:^{10,18,19,20}

A. TURBIDITY MEASUREMENT:

It is parameter for determining the droplet size and self emulsification time. A fixed amount of SMEDDS is added to a fixed quantity of suitable medium (0.1N HCL or phosphate buffer) under continues stirring at 50 rpm on magnetic stirrer at optimum temperature and turbidity is measured using a suitable turbidimeter. The optical density is measured periodically to determine the clarity of microemulsion formed as well as the emulsification time.

B. VISUAL EXAMINATION:

The assessment of self emulsification is possible by visual evaluation. After dilution of SMEDDS with water, opaque and milky white appearance indicates the formation of macroemulsion where as the clear isotropic transparent solution indicate the formation of microemulsion.

C. DROPLET SIZE ANALYSIS:

The droplet size is mainly dependent on the nature and concentration of the surfactant. The microemulsion which is formed upon dilution with water produces droplets of very narrow size and size distribution for effective drug release. Photon correlation spectroscopy, dynamic light scattering or laser diffraction techniques are used to determine the droplet size of emulsion

D. ZETA POTENTIAL MEASUREMENT:

Zeta potential helps to predict the stability and flocculation of the emulsion system. The stability of the emulsion is directly related to the charge present on the surface. Zeta sizer, mastersizer, etc are often used to determine the zeta potential. Zeta sizer uses the light scattering technique to determine the globule size, zeta potential and molecular weight of nano particulate systems. Higher zeta potential indicates the good stability of the formulation. Positively charged droplets have the property interact efficiently with the mucosal surface of the GIT.

E. SELF EMULSIFICATION TIME:

The self emulsification time is determined using USP dissolution apparatus 2 at 50rpm. Here 0.5g of SMEDDS is introduced into 250ml of 0.1N HCL or 0.5% at room temperature. The time for self emulsification of the system is noted. Rate of emulsification is depends on nature of oil phase and oil/surfactant ratio. Rapid rate of emulsification is obtained with high surfactant concentration because of rapid ejection of oil droplets by penetration of water into the interface

F. CLOUD POINT DETERMINATION:

Cloud point is usually determined by increasing the temperature of water bath in which the formulation is placed. The point where the percentage transmittance decreases and above which the transparent solution changes to cloudy solution will signify the cloud point. As the body temperature is 37°C, formulation should exhibit the cloud point more than the body temperature to exhibit the self emulsification property.

G. THERMODYNAMIC STABILITY STUDIES:

The physical stability of the formulation is important as it is adversely affected by the

precipitation of the drug in excipient matrix. Poor physical stability of the formulation lead to phase separation, the instability affects the bioavailability as well as therapeutic efficacy.

The following cycles are used for thermo dynamic studies:

Heating cooling cycle: six cycles between 4°C to 45°C, keeping at each temperature for not less than 48hr is studied. Those formulations which are stable are subjected to centrifugation test.

Centrifugation:

The samples were centrifuged between 26°C and +25°C, keeping at each temperature for not less than 48hr is done at 3500 rpm for 30min. These formulations which doesn't show any phase separation are taken for freeze thaw stress test.

Freeze thaw cycle: Freeze thaw cycling between -25°C and 25°C keeping at each temperature for not less than 48hrs. Sample with no existence of phase separation, cracking or creaming is an indication of good stability.

H. REFRACTIVE INDEX AND PERCENTAGE TRANSMITTANCE:

The refractive index is studied using Abbe refractometer by placing one drop of solution on the slide. Percentage transmittance of the system is measured at 650 nm using U.V spectrophotometer using distilled water as a blank.

I. DISPERSIBILITY TEST:

The dispersibility test for SMEDDS is carried out to assess the capability of the formulation to disperse into emulsions, consists of globules of suitable nano size. It is carried out using a standard USP dissolution apparatus ???. Here 1ml of each formulation added to 500ml of water at $37 \pm 0.5^\circ\text{C}$ at a stirring speed of 50rpm/min. upon mixing with water, any of the following observation can be seen which has been mentioned in table 6:

TABLE 6:

MIXTURE/GEL	TYPE OF FORMULATION
Transparent mixtures	microemulsion
Transparent gel	micro emulsion gel
Milky or cloudy mixture	emulsion
Milky gel	emulgel

J. DILUTION:

When emulsion upon dilution with various dissolution medias, should not show any phase separation or precipitation of drug even after 12hr

of storage, that formulation is considered as robust to dilution.

K. IN VITRO DIFFUSION STUDY:

This study is done to determine the release behavior of drug from the formulation, where phosphate buffer is generally used as dialyzing medium. In this method 1ml of SMEDDS formulation along with 0.5ml of phosphate buffer is filled in a dialyzing membrane. It is placed in the dissolution apparatus, at a rotating speed of 100rpm. Samples are withdrawn at different time intervals and then after suitable dilution are analyzed for the drug release. Equal volume of fresh buffer is replaced to maintain sink conditions.

L. IN VITRO DISSOLUTION TECHNIQUE:

The quantitative in vitro dissolution studies are carried out using USP dissolution apparatus type ?? to assess the drug release from oil phase into aqueous phase. The procedure involves placing SMEDDS formula into 500 ml of simulated gastric fluid containing 0.5% w/v of SLS rotated at 50 rpm and maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. Aliquots of sample are withdrawn at regular intervals of time and volume withdrawn is replaced with fresh dissolution medium. Samples taken are then analyzed by U.V. spectro-photometry.

APPLICATIONS OF SMEDDS:^{21,22}

IMPROVEMENT OF SOLUBILITY:

By formulating the drug in the form of SMEDDS will bypass the dissolution step in case of class 2 drugs (low solubility/high permeability). In SMEDDS, the lipid interacts readily with water, forms fine particulate o/w emulsion. Poorly water soluble drug, for ex: candesartan cilexetil, is formulated as SMEDDS and is filled directly into hard gelatin capsules for oral administration. The results showed that SMEDDS has enhanced the solubility and dissolution profile of Candesartan cilexetil.

ENHANCED BIOAVAILABILITY:

In SMEDDS, the lipid matrix will interact readily with water and forms fine oil in water emulsion (o/w). This emulsion will deliver the drug in the dissolved state, which are readily absorbed results in increase in the AUC i.e, bioavailability and Cmax.

Ketoprofen, a moderately hydrophobic drug it has low solubility and irritates the gastric mucosa drug chronic therapy when this is formulated into SMEDDS it increases the solubility and bioavailability which minimizes the drug irritation.

PROTECTION AGAINST BIO DEGRADATION:

Many of the drugs are degraded in the GI tract because of acidic pH in the stomach, enzymatic degradation, and hydrolytic degradation. When such drugs are formulated in the form of SMEDDS, the drug will be protected against degradation, as liquid crystalline phase might act as barrier between degrading environment and the drug. Acetyl salicylic acid is a drug that degrades in the GI tract was formulated as lipid matrix and compared with the commercial formulation. Lipid formulation exhibited a good plasma profile and the bioavailability was increased to 73%. This suggests that SMEDDS has capability to protect the drug from degradation.

SUPERSATURABLE S-SMEDDS:

Generally high concentration of surfactant causes gastric irritation. To decrease the side effects of surfactant and to achieve rapid absorption of poorly water soluble drugs, S-SMEDDS are developed. The S-SMEDDS is an approach to generate the super saturated solution of drug when the formulation is released from a appropriate dosage form into the aqueous medium and also increases the driving force for crossing biological barrier.

RECENT TRENDS IN SMEDDS:²⁰

Self emulsifying sustained/ controlled release tablets
Self emulsifying capsule

Self emulsifying sustained/ controlled release pellets

Self emulsifying beads

Self emulsifying sustained release microspheres

Self emulsifying suppositories

Self double emulsifying drug delivery system

Solid-self emulsifying drug delivery system

Self microemulsifying floating delivery system

Self microemulsifying mouth dissolving films

Self emulsifying nano particles

CONCLUSION:

SMEDDS is an approach for formulating of drug compounds with poor aqueous solubility, high

molecular weight, poor systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution and low bioavailability. Faster and enhanced drug release can be attained with the smaller droplets which in turn promote the bioavailability. The present review highlights the developmental steps (solubility studies, construction of ternary phase diagram and various evaluation tests), involved in obtaining the robust and stable dosage form. Thus SMEDDS can be potentially used for the delivery of BCS class 2 and 4 drugs.

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